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The Effect of Drugs on the Longitudinal and Circular Muscle of the Rabbit's Intestine: A New Method of Study

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LOYOLA UNIVERSITY

THE EFFECT OF DRUGS
ON THE LONGITUDINAL AND CIRCULAR
MUSCLE OF THE RABBIT'S INTESTINE;
A NEW METHOD OF STUDY

A THESIS
SUBMITTED IN PARTIAL FULFILMENT
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BY
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INTRODUCTION

This study is an out growth of previous work done in this laboratory on the effect of varying inorganic ions on intestinal activity, Spiteri (1931). At that time excised intestinal segments were used and the movements of only the longitudinal muscle were recorded. However, in many cases there was apparent considerable activity which could not be recorded. This led us to feel that if the movements of both the longitudinal and circular muscular coats were recorded, the record would be more representative of what was actually occurring in the segment.

A search of the literature revealed that some previous work had been reported on the activity of both muscular coats of the intestine, Bayliss and Starling (1899), Trendelenburg (1917), Hockett and Thienes (1929). In this work, however, there was some variations in descriptions of the movements of the intestines, and also in drug action so that a new method of recording intestinal activity which would perhaps give additional information was developed.

This present study upon the action of a number of drugs on the longitudinal and circular muscles of the rabbit's intestine was undertaken then since it appeared that such a study might be useful in establishing a basis for comparing later work to be done on inorganic ions.

METHOD AND MATERIALS

The apparatus used in our studies is a combination of methods used by several previous investigators working on excised intestinal strips. The Trendelenburg method (1917) of recording changes in the volume or pressure of an intestinal segment by means of a water manometer and a lever to record movements of the longitudinal muscle was used as a basis for our apparatus. To it was added a modification of the enterograph of Bayliss and Sarling (1899). This apparatus consisted of levers which were fastened to the intestinal strip and by placing these at right angles to each other they were able to record both longitudinal and circular movements.

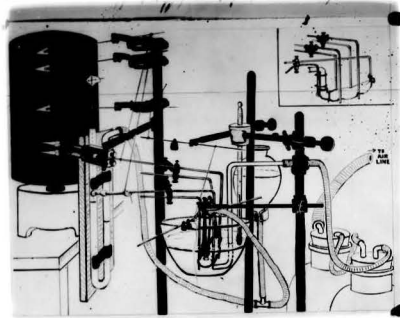


Fig. 1

The apparatus used in our studies is diagramed in fig. 1. In the upper right hand corner of fig. 1 is inserted a diagram showing the detail of connecting the intestinal strip to the lever and to a glass cannula leading to the pressure or volume recording manometer. The levers are modified heart levers with two arms of aluminum wire 1/16 inch in diameter. A movable arm passes through the axis-spindle and can be adjusted as to length by means of a set screw arrangement. The lower arm is fastened to the axis support and is stationary or immovable except that its length may also be varied by means of a set screw. Both arms are bent at right angles to allow proper adjustment to the intestinal strip.

The method of placing an intestinal strip in the apparatus consists first in tying a small glass bead into the proximal end of the segment which is about 2 inches long, and this end is then made fast to the movable arm of the lever. The other end of the intestine is slipped over a glass cannula attached to the immovable arm, and tied to it. This lever records the longitudinal movements. The cannula is connected to the leveling bulb and water manometer, and records pressure or volume changes of the segment. Two other levers are set across the intestine at right angles to the first lever being placed about 2 cm. apart and balanced so as to just touch the intestine at all times, and thus record circular movements.

On the larger part of fig. 1 the complete apparatus is shown. The movable lever arm used for longitudinal movements

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is connected with a second lever directly above by silk thread. This second lever in turn is attached to a writing lever which is adjusted to the kymograph. A contraction of the longitudinal muscle is recorded by an upward line on the tracing. The two levers placed across the intestine are attached by threads directly to the writing levers. It will be seen that the records of movements are here reversed, i.e. contraction of the circular muscle causes a fall in the writing points.

The cannula to which is tied the lower end of the intestinal segment is shown in fig. 1 connected by rubber tubing with a leveling bulb and to a water manometer. This arrangement makes it possible to alter the intra-intestinal pressure by means of the leveling bulb; and the manometer records changes in pressure or volume of the intestine in different stages of activity. Tyrode solution as described below was used in the liquid system. In tying the intestinal segment to the cannula care was taken to prevent any air bubbles from entering the segment with the Tyrode solution. After the strip had been properly adjusted the leveling bulb was set at a definite position so as to give a pressure of 16-20 mm. of water and the exact pressure used was recorded. The tube leading to the leveling bulb was then clamped off. A signal magnet and a time marker complete the tracing.

The salt solution we have employed in all of our work is the Tyrode solution given by Sollmann and Hanzlik (1928) slightly modified. It had the following composition:

NaCl	.8	gm.
KCl	.02	"
CaCl ₂	.01	"
NaHCO ₃	.015	"
MgCl ₂	.01	"

Dist. water q.s. 100 cc.

This solution differs from the original Tyrode in that the original contains NaHCO₃ .1%, NaH₂PO₄ .005% and glucose .1%.

NaH₂PO₄ was omitted since we regulated the pH in another manner given below, and to remove any possibility of the phosphate ions producing an effect with the drugs. The amount of NaHCO₃ was reduced to lower the pH to about 7.4. Glucose was omitted since we found that its removal had no apparent effect upon the activity of the intestine for the length of time strips remain in the bath.

This modified Tyrode solution has a pH of approximately 7.4. This is kept constant throughout the experiment by using the method described by Thomas (1931). The air used for aerating the bath is passed through two washing bottles containing powdered magnesium carbonate and solutions of phosphate buffers. The tops of the bottles are shown in the lower right hand corner of fig. 1. The principle of the method is a constant CO₂ liberation from the MgCO₃ using a phosphate buffer solution--a change of this giving a corresponding change in CO₂ liberation. With the maintenance of this constant concentration of CO₂ the air passing through the buffer solution can be brought to a definite CO₂.

tension and this in turn will maintain a constant CO_2 tension in the bath and thus a constant pH. We have frequently checked the pH of the Tyrode bath by colormetric means and have found it to be efficient in maintaining a constant hydrogen ion concentration.

In the setup the strip to be studied is immersed in a bath containing 300 cc. of the modified Tyrode solution which is kept at a constant temperature of 37 C. by a water bath heated by a microburner. Drugs are added to the bath in .1% aqueous solution. The amount of drug solution used, 3 cc. or less in most cases, is too small to materially alter the salt concentration of the bath. The Tyrode solution of the bath may be removed by suction and fresh solution added with out disturbing the apparatus.

For our studies rabbits were used. Young healthy animals weighing from 1500 to 2000 gms. were selected and their food intake regulated. The diet consisted of oats and hay with the addition twice a week of some fresh green food. The time of the last feeding was recorded for each animal used.

Alvarez (1914) has demonstrated a slower rhythmic rate, but a greater amplitude for the ileum than for the other levels of the small intestine. Alvarez (1929) has also shown that in the last 25 cm. of the ileum the rhythmic rate may rise somewhat and peristalsis may be reversed. For these reasons the segments used in our studies were taken from 30 to 50 cm. oral from the iliocecal junction.

The animals were killed by a blow at the base of the skull

The abdomen was opened and the intestine cut free from its mesenteric attachment and was placed immediately in Tyrode solution. Segments may be kept in this way at a low temperature for hours with but slight quantitative alteration in movements or response to drugs. A record was kept of whether the strip was used at once after removal or after a period of time.

RESULTS

The drugs used in our studies were pilocarpine, acetylcholine and eserine. In many respects the results obtained were similar for the different drugs, although some qualitative differences were observed. An attempt was made in each experiment to correlate the graphic record obtained with the visible changes occurring in the segment in the bath. The various types of graphic records obtained are presented in Charts A to H. Table I gives data pertaining to these Charts.

Table I (Normal Movements)

Graph	Hrs. Fast	Longitud. Muscle			Circular Muscle			Perist.	Press.
		Tone	Rhythm	Ampl.	Tone	Rhythm	Ampl.		
88	36	lev.	8	5.3cm	lev.	8	1.3cm	-	15mm
38	4	fall.	10	1. " "	rise.	10	.3 "		10 "
86	48	irr.	8	4.5 "	irr.	8	.5 "	-	15 "
40	4	irr.	13	3.0 "	irr.	13	.5 "		7 "
42	48	fall.	10	1.2 "	rise.	10	.4 "	-	10 "
64	18	rise.	10	2.0 "	fall.	10	.8 "		20 "
62	4	fall.	9	1.1 "	rise.	9	.3 "		20 "
79	48	lev.	8	5.0 "	lev.	8	.6 "	-	20 "
78	24	fall.	8	3.5 "	rise.	8	1.1 "		20 "
65	4	rise.	7	5.8 "	fall.	7	2.0 "	-	20 "
75	48	lev.	7	9.0 "	lev.	7	1.4 "	-	20 "
77	24	irr.	8	1.8 "	irr.	8	.4 "		30 "
82	42	irr.	8	4.9 "	irr.	8	.9 "	-	20 "
86	48	fall.	8	2.0 "	rise.	8	1.4 "	-	20 "

Longitud.: -longitudinal

Hrs. Fast.: -hours animals are fasted previous to experiment

Ampl.: -amplitude

Perist.: -peristalsis present

Press.: -pressure in mm. of water

lev.: -level tone

fall.: -falling tone

rise.: -rising tone

irr.: -irregular tone

Table I (After Drug)

Graph	Drug	Conc.	Longitud. Muscle			Circular Muscle					
			Tone	Rhythm		Tone	Rhythm			Perist.	Press.
				Rate	Ampl.		Rate	Ampl.			
88	P.	1:5000000	rise,	8	2.3cm	fall.	8	.6cm	-	17mm	
38	P.	1:5000000	m.e.	11	.1 "	rise.	11	.5 "		12 "	
86	P.	1:5000000	m.e.	8	6.7 "	rise.	8	.8 "		17 "	
40	P.	1:100000	rise.	12	2.0 "	fall.	12	.5 "		12 "	
42	P.	1:100000	fall.	-	-	s.t.	-	-	-	27 "	
64	A.C.	1:500000	rise.	5	1.3 "	fall.	5	.5 "		28 "	
62	A.C.	1:500000	fall.	-	-	rise.	10	1.1 "		22"	
79	A.C.	1:5000000	rise.	9	7.2 "	fall.	9	1.1 "	-	22 "	
78	A.C.	1:5000000	m.e.	9	1.2 "	rise.	9	.3 "		22 "	
65	A.C.	1:5000000	rise.	9	1.0 "	fall.	9	.2 "		22 "	
75	E.	1:3000000	rise.	8	1.5 "	fall.	9	1.0 "	-	20 "	
77	E.	1:4000000	fall.	-	-	rise.	-	-		30 "	
82	E.	1:5000000	rise.	8	2.8 "	fall.	8	.7 "		20 "	
86	E.	1:5000000	fall.	10	1.7 "	rise.	10	1.4 "		20 "	

Abbreviations same as in the preceeding part of table with the following additions:

Conc.: -concentration of the drug

P.: -pilocarpine

A.C.: -acetyl choline

E.: -eserine (physostigmine)

m.e.: -mixed effect

s.t.: -secondary tone changes

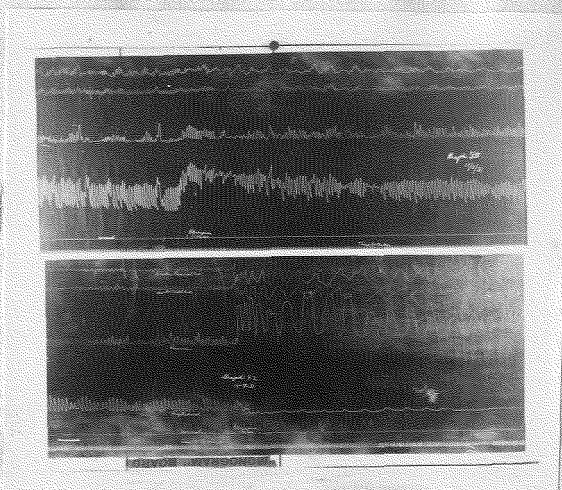


Chart A--Graphs 40 and 42

Chart A shows two types of reactions obtained with pilocarpine hydrochloride (Merck) in a concentration of 1:100,000. The upper tracing, graph 40, shows a sudden increase of longitudinal muscle tone following the drug. Rhythmic movements remained much the same in this preparation. Circular muscle tone relaxed. The pressure increased with the increased longitudinal tone. Graph 42 of the same Chart shows a sudden increase of circular tone with development of periodic tone waves. Rhythmic activity was lost after the addition of the drug. The longitudinal tone fell as the circular tone increased. The periodic tone changes of the circular muscle appeared in the segment as local non-moving segmentation waves. The pressure varied as the circular tone waves appeared. Some interesting differences appear in the normal movements shown in these two graphs. The longitudinal movements of graphs 40 are strong

rhythmic contractions with an even tone whereas the corresponding movements of graph 42 are of smaller amplitude, slightly irregular and the tone falls slowly. The normal circular movements of graph 40 show gradually relaxing tone while the circular tone of graph 42 is even up until the time the drug is added.

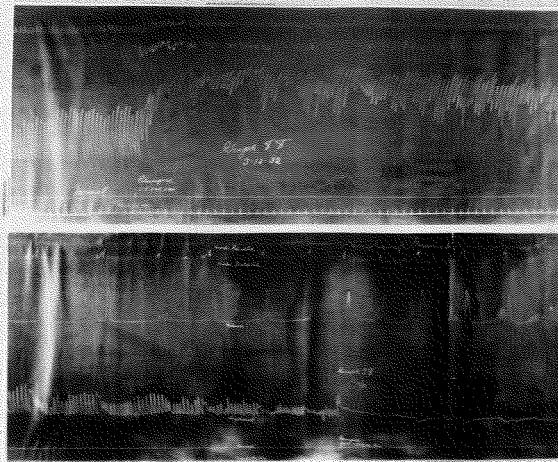


Chart B--Graphs 88 and 38

Chart B shows similar types of action obtained with pilocarpine in the concentration of 1:5,000,000. Graph 88 shows increased longitudinal and decreased circular muscle tone after the addition of the drug. In this case rhythmic movements persisted in both coats and no periodic tone changes developed in the circular muscle. The normal movements in this preparation were regular with an even tone. Graph 38 shows the second type of reaction, i.e. an increased circular tone with a decreased longitudinal tone and suppression of rhythmic movements in the longitudinal record. The peristaltic movements shown in the graph became more frequent after the addition of pilocarpine. As is the usual case with segments showing peristalsis, the the longitudinal tone was irregular and fell prior to the addition of the drug.

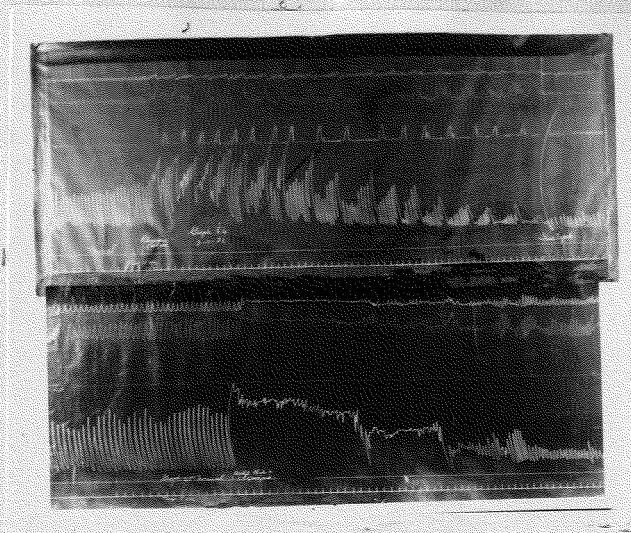


Chart C--Graphs 86 and 65

Chart C, graph 86 shows the third type of reaction which we term a "mixed effect". Pilocarpine 1:5,000,000 caused in this segment an initial rise in longitudinal tone with some inhibition of circular tone. Peristalsis developed almost at once and the longitudinal tone fell as the circular tone increased. Rhythmic movements persisted after the addition of the drug. Examination of the normal movements showed slight irregularities of tone in both coats.

The action of Pilocarpine of various concentrations was studied on 31 preparations, of this number 18 responded by an increase in longitudinal tone, 10 showed a decrease in longitudinal tone, 3 exhibited various degrees of the mixed effect.

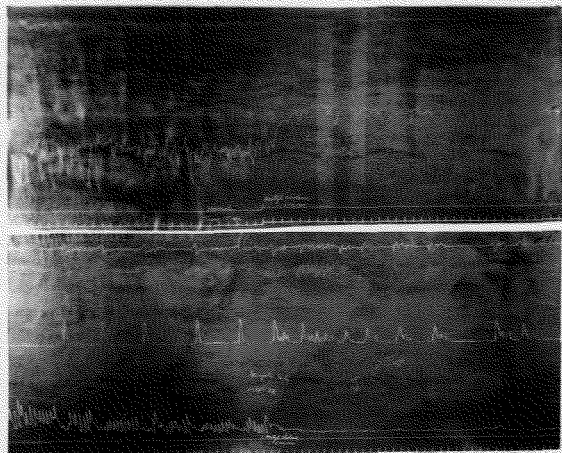


Chart D--Graphs 64 and 62

Chart D shows two types of response obtained when acetyl choline (Eastman) was used in the concentration of 1:5,000,000. Graph 64, the upper tracing, shows a marked increase in longitudinal tone following the addition of the drug. The circular tone was inhibited. Rhythmic movements appeared depressed in both coats. The initial movements in this segment were irregular and the longitudinal tone was increasing. Graph 62 of Chart D shows a depression of longitudinal tone and an increase of circular tone after the addition of acetyl choline. Rhythmic movements were lost in the longitudinal muscle after the addition of the drug. The increased amplitude of movements shown in the circular tracing was due to the rapid peristaltic-like waves. It will be seen that each circular movement after the addition of the drug was accompanied by changes in the intra-intestinal pressure or volume. Toward the latter portion of the

tracing periods are seen in which both coats are motionless. Examination of the movements previous to the addition of the drug in this graph shows peristalsis occurring and the longitudinal tone falling.

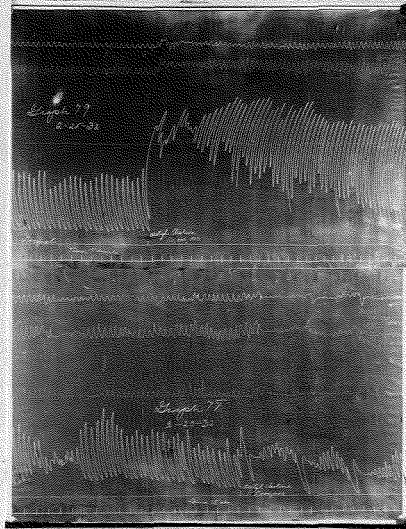


Chart E--Graphs 79 and 78

Chart E is of two preparations in which acetyl choline was used in 1:5,000,000 concentration. The upper tracing, graph 79, shows a marked increase of longitudinal tone with an inhibition of circular tone after the addition of the drug. The rhythmic movements after a brief period became even greater in amplitude than before the addition of the drug. The normal movements in both coats were regular and even in both rhythm and tone. Graph 78 of the same chart shows a different type of reaction. The longitudinal tone here underwent a slight rise followed by a rather rapid fall. Peristalsis was initiated as the circular tone became augmented. Irregularities in rhythm appeared in both coats before the addition of the drug. The longitudinal tone was falling when the acetyl choline was added. Graph 65 of Chart C is of a segment which showed a mixed effect after the addition of the acetyl choline 1:5,000,000. The sudden rise

in longitudinal and inhibition of circular tone was followed immediately by a rapid fall of longitudinal and increase of circular tone. Two peristaltic movements developed as the longitudinal tone fell.

Acetyl choline was used on 23 preparations, 15 of which responded by an increased longitudinal tone. Four showed a decrease in longitudinal tone and 4 showed a mixed reaction. The solutions of acetyl choline were made up fresh for each experiment.

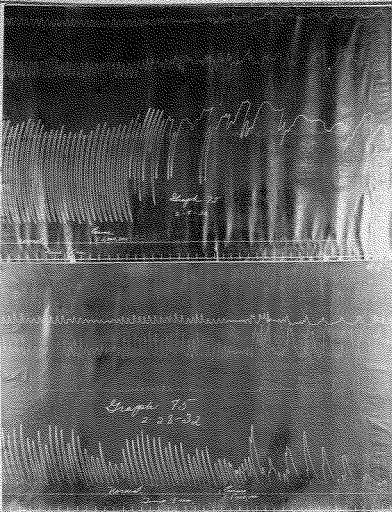


Chart F--Graphs 75 and 85

Chart F is of two preparations upon which eserine salicylate (Merck) was used. The upper tracing, graph 75, shows a marked increase of tone after the addition of eserine 1:3,000,000. The initial activity in this strip was strong and even in both the circular and longitudinal muscle. The increased longitudinal tone after the addition of the drug was slow to be lost as shown by the interval which elapsed before the original tone level was again reached. Periodic tone changes were initiated in both coats by the drug, and rhythmic movements were irregular and decreased in amplitude.

Graph 85 of chart F shows the reaction of a strip to eserine 1:5,000,000. In this segment peristalsis was occurring before the drug was added. These movements became more frequent after the addition of the drug, but rhythmic movements were largely lost. The circular tone was somewhat increased and the

longitudinal tone depressed by the drug.

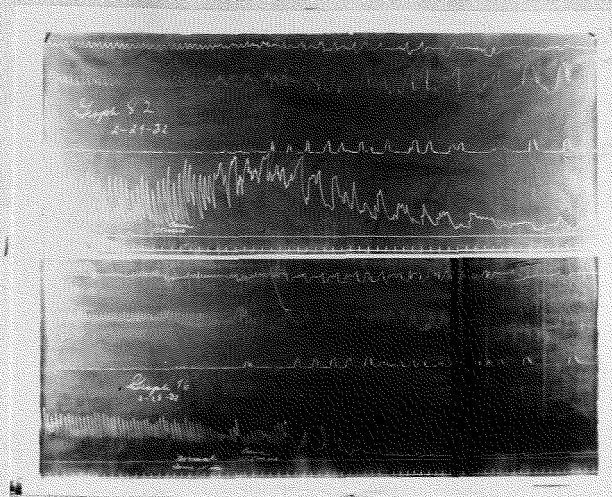


Chart G--Graphs 82 and 86

Graph 82 of Chart G shows a mixed response to eserine 1: 5,000,000. The initial movements of this strip were irregular. The drug caused a slight rise in the longitudinal tone followed by a rapid fall. The circular tone was inhibited for a brief period after the addition of the drug, but soon developed rapid periodic variations and became stronger than before the addition of the drug. Inhibition of rhythmic movements was seen in both coats. Graph 86 of the same chart shows the depressed response of the longitudinal coat after the addition of eserine 1: 5,000,000. The tracing here is very similar to that in graph 82 except that no transitory rise in longitudinal tone occurs. In both graphs the effect of the periodic tone changes of the circular muscle in changing the intraintestinal pressure or volume is seen.

Of 11 preparations upon which eserine was used only 3

showed a lasting increase in longitudinal tone, 3 showed a transitory rise or mixed effect, and 5 showed a depression of longitudinal tone without an initial rise.

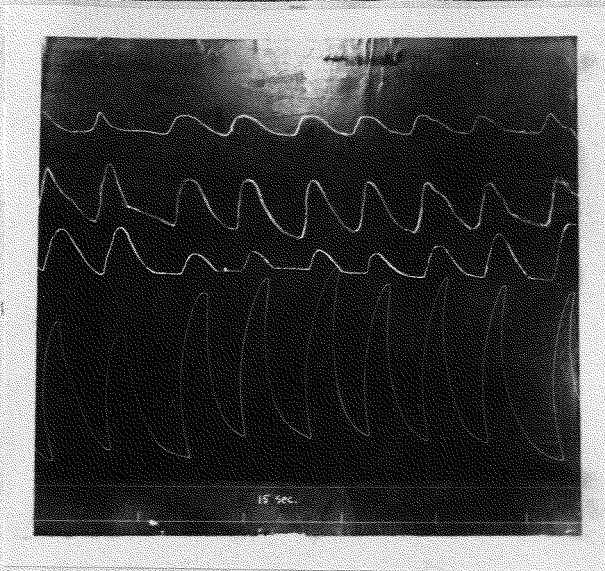


Chart H

Chart H shows the rhythmic activity of the intestine as recorded on a rapidly moving drum. The form of the curve is similar on all four records. It will be seen that the time required for circular muscle contraction corresponds to that required for longitudinal relaxation.

DISCUSSION

Several investigations upon the question of reciprocal activity of the longitudinal and circular coats of the intestine have appeared in the literature. Exner (1884) from a structural consideration of the intestine concluded that contraction of the longitudinal muscle shortens the intestine and widens the lumen, while contraction of the circular coat lengthens the tube and narrows the lumen. Bayliss and Starling (1899) report, "By registering the contractions of the two coats by means of two enterographs at right angles to one another, it may be shown that the two coats, if they contract at all always contract at the same time." They believed the purpose of the longitudinal muscle contraction was to afford protection for the circular muscle. Magnus (1904) held that contraction of the intestinal tube required the relaxation of the longitudinal muscle, but that the lumen was diminished by contraction of the circular muscle. He held that the lengthening of the longitudinal muscle was passive from the strong contraction of the circular muscle. More recently Inoue (1922) recorded both circular and longitudinal activity in segments of rabbits' intestines by suspending the strips from threads attached so as to pull upon writing levers when either coat contracted. This worker found that contraction of one coat is usually accompanied by relaxation of the other. Using drugs, he found that with small doses of pilocarpine the longitudinal muscle was contracted and the circular muscle relaxed--

larger doses produced only a temporary contraction of the longitudinal muscle and relaxation of the circular muscle. This effect was followed by a persisting, gradually increasing circular tone. Inoue noted, however, that after physostigmine, both coats may become contracted at the same time. Hockett and Thienes (1929) using excised guinea-pig intestines found a reciprocal activity of the two coats in a majority of cases. In a few cases where reciprocal activity did not exist it could be initiated by treating the segments with nicotine and atropine.

A study of the graphic records obtained in our work serves to illustrate that the apparatus we have used will record simultaneously circular and longitudinal muscle activity of the isolated intestine. The greater number of graphs obtained show activity in both coats. In these cases, if the activity is of a simple rhythmic type, the tracings obtained from the two coats are similar--both as to the form of the curve for the individual rhythmic movement and the rate of rhythmic movements. In other instances such as graphs 42 and 86 after drugs had been used, it is possible to show well marked activity in the circular coat without any evidence of movements in the longitudinal. Irregular tendencies sometimes appeared in the tracing of one coat without altering the regular rhythmic movements of the other. From a consideration of our results it would seem that a normal reciprocal activity of the two coats exists during simple rhythmic movements. The form

of the curve produced shows the contraction of the circular coat in this type of movement is slow corresponding with the time duration of longitudinal relaxation. Under certain conditions the circular muscle may contract abruptly as when peristaltic movements occur. In the case of peristalsis the normal time relation of activity of the two coats seems to be altered. It is often possible during peristalsis to observe the longitudinal muscle maintaining a contraction while the circular muscle is also contracted. We have, also, noted that the longitudinal muscle relaxes slightly before the circular muscle during the passage of a peristaltic wave. It would seem, therefore, that mechanical effects tending to elongate the intestine by contraction of the circular muscle could not adequately account for the depression in longitudinal tone obtained by us in many preparations after a drug. Also it would seem impossible on the basis of reciprocal activity alone, whether mechanical or otherwise, to account for the variations observed in response to drugs.

Granting that under certain conditions the contraction of one coat might mechanically prevent the contraction of the other, we must still find why all segments do not react alike. Attempts to correlate the results of our experiments with such factors as type of initial rhythmic movement, period of starvation of the animal, etc., have failed.

We have noted, however, a constant feature as regards initial tone of the longitudinal muscle. In all experiments in

which the segment reacted to a drug by a decrease of longitudinal tone, examination of the longitudinal tone previous to the addition of the drug showed the tone to be falling. In those segments reacting to the drug by an increase in longitudinal tone the initial tone was found to be level or increasing. The circular tone appears to have been reciprocally relaxed or contracted to the condition of the longitudinal tone. It is possible that the initial tone of the two muscular coats is associated with their ability to respond to drugs. If the tone of the longitudinal muscle is falling, the level tone of the circular muscle would allow it to strongly contract, and as a result of this might prevent any delayed contraction of the longitudinal muscle. On the other hand, if the initial longitudinal tone of the strip was level or increasing, it might be associated with a higher degree of ability to respond to the drug and as a result the drug might produce a strong contraction of the longitudinal muscle which would tend to prevent circular muscle contraction.

The mixed effect produced by the drugs on certain segments may have been due to the rate of drug penetration through the intestinal wall. Inoue (1922) believes that the first action of drugs added to a bath containing an intestinal segment is upon the longitudinal coat since it is most superficial. Later the drug reaches the more deeply placed circular coat and is able to act there. The delayed contraction of the circular coat, this author believes, brings about the relaxation

of the longitudinal muscle.

Another possible explanation of our various results lies in the reversal of drug action reported by a number of investigators. Sollmann (1922) in his review of the pharmacology of the autonomic nervous system calls attention to numerous examples of reversal of drug action. He points out that reversal of function may be the result of either transposition of action, i.e. action of a drug upon a system other than the normal, or transformation of action, i.e. the action being upon the normal system but in a direction opposite of the normal. Le Heux (1918) attributed the variable responses of the intestine to atropine to the amount of choline naturally present in the intestine.

Asher and Sheinfinkel (1927) were able by treating the isolated frog's heart with certain substances to change the physiological condition so that atropine excited the vagus instead of its usual inhibitory effect. Inoue (1922) working on the response of rabbit's intestines to drugs found in one case an apparent reversal of action in a rundown animal. He attributed the resulting depression following pilocarpine to the poorly developed longitudinal muscle coat. Mc'Crea and Macdonald (1929) recording effect of drugs on ento-gastric pressure, found that pilocarpine, physostigmine and acetylcholine may act either as augmentors or depressors of ento-gastric pressure, the result being dependent on the initial condition of tonus. These workers also call attention to

persisting after-contractions set up by pilocarpine and physostigmine similar in appearance to the secondary tone changes we have noted appearing in the circular muscle of the intestine following these drugs. Hockett and Thiemes (1929) found that in a majority of cases pilocarpine relaxed the longitudinal muscle and contracted the circular muscle of guinea pig intestines. This statement we interpret as indicating that they obtained the opposite result in some cases.

At the present we are unable to say what mechanism is acting to produce the variations we have noted in the response of intestinal segments to drugs. It should be emphasized, however, that our results all showed one common feature, i.e. a stimulation of one of the two intestinal coats in each case, and further that the coat not reactive by stimulation showed inhibition.

CONCLUSION

1. A method for simultaneously recording movements of the circular and longitudinal muscles together with changes in intra-intestinal pressure or volume of excised segments of rabbits' intestines is described.

2. From a study with this apparatus it appears that a reciprocal activity exists in the two coats of the intestine during simple rhythmic movements, but that this reciprocal activity may be altered during certain other types of movement.

3. Using pilocarpine, acetyl choline and eserine, it was found that the longitudinal muscle tone might be augmented or inhibited, and that the circular muscle tone was augmented when the longitudinal tone was inhibited or that the circular tone was inhibited when the longitudinal tone was augmented. A mixed type of response to these drugs is also described.

4. Possible explanation for the variations noted in response to these drugs is discussed.

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